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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/813,745	03/31/2004	Mathai Mammen	P-162-US1	5848

27038 7590 02/13/2007  
THERAVANCE, INC.  
901 GATEWAY BOULEVARD  
SOUTH SAN FRANCISCO, CA 94080

EXAMINER
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SEAMAN, D MARGARET M

ART UNIT	PAPER NUMBER
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1625

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/13/2007	PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

## Office Action Summary

Application No.

10/813,745

Applicant(s)

MAMMEN ET AL.

Examiner

D. Margaret Seaman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 23 October 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-39 is/are pending in the application.
- 4a) Of the above claim(s) 1-18 and 20-39 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 19 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☒ Claim(s) 1-39 are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- ☐ Notice of Informal Patent Application
- ☐ Other: \_\_\_\_\_

### DETAILED ACTION

1. Applicant's election with traverse of group 1 in the reply filed on 10/23/2006 is acknowledged. The traversal is on the ground(s) that there is no serious search burden on the examiner since the groups I-III have the same common core and utility. This is not found persuasive because the argument of a common core and utility is valid as far as a Lack of Unity of Invention, which this case is not filed under 35 USC 371. Further, the search for all groups is burdensome to the examiner since the groups I-III all have different classifications. This equates to a search burden.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-18 and 20-39 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 10/23/2006.

3. This application contains claims drawn to an invention nonelected with traverse in Paper dated 10/23/2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

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4. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

*Claim Rejections - 35 USC § 112*

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 19 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds wherein R4 is alkylene, does not reasonably provide enablement for R4 being all other R4 moieties such as alkenylene-heteroarylene-O-alkynylene-N(Qj)C(O)O-alkenylene-thereocyclene-alkylene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The only examples provided by the instant specification, namely examples 1-20 have R4 being alkylenylene which is optionally substituted. The closest prior art is where the equivalent to the instant R4 is alkylene of 1-3 carbon atoms. It is not seen where the instant specification teaches how to make use or choose R4 moieties other than alkylene.

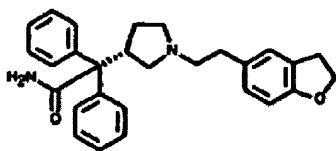
There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue".

These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

- 1) The breadth of the claims,
- 2) The nature of the invention,
- 3) The state of the prior art,
- 4) The level of one of ordinary skill,
- 5) The level of predictability in the art,
- 6) The amount of direction provided by the inventor,
- 7) The existence of working examples,
- 8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

**The nature of the invention:** The nature of the invention is the compounds that are useful to treat a disorder that is modulated by the muscarinic acetylcholine or B-adrenoceptor receptor.

**The state of the prior art:** The state of the prior art is compounds similar to



that have activity as B-adrenoceptor or muscarinic

acetylcholine receptor that are useful to treat bronchial asthma. The pharmaceutical art involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

**The predictability in the art:** It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not

permit a single extrapolation of *in vitro* assays to human diagnostic efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). In the instant case, the instantly claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to the therapeutic effects of all diseases, whether or not the modulation of muscarinic acetylcholine receptor or B-adrenoceptor receptors would make a difference in the disease. Hence, in the absence of a showing of a nexus between any and all known diseases and the modulation of muscarinic acetylcholine receptor or B-adrenoceptor receptors, one of ordinary skill in the art is unable to fully predict

possible results from the administration of the compound of claim 19 due to the unpredictability of the role of modulation of muscarinic acetylcholine receptor or B-adrenoceptor receptors.

**The presence or absence of working examples:** The compounds made by the instant specification have only R4 being alkylene of up to 10 carbon atoms. The specification speaks of Table I and Table II which have more examples (up to 300 more examples) of compounds made by the instant specification, but the instant specification does not contain tables I or II. The "working" examples disclosed in the specification describe tests that the instant compounds could be tested in. However, the tests described appear to be prophetic tests and not actual tests performed on the instant compounds.

**The amount of direction or guidance present:** The guidance present in the specification is that of the compounds work. However, Milecki (J Med Chem, Vol 30(9), 1987, pp 1564) teaches that compounds having pure agonist or antagonist activity on the B-adrenoceptor have no obvious advantage as drugs. On the other hand, pure agonist or antagonist activity is highly desired in the probes used for molecular characterization of B-adrenoceptors. Zlotos (Exp Opin Ther Patents, Vol 9(8), pp 1029, 1999) teaches that four different subtypes of the muscarinic acetylcholine receptor are known to exist and all these muscarinic agonists and antagonists in clinical practice only show very weak selectivity. Further, the pharmacological findings will need more research work to become established in clinical trials. The specification does not seem



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to enable a correlation between the muscarinic acetylcholine receptor or B-adrenoceptor receptors and the treatment of diseases.

**The quantity of experimentation needed:** The quantity of experimentation needed is undue. One skilled in the art would need to determine what R4 moieties of the many encompassed by the instant claim 19 have efficacy to treat diseases that would be benefited by the muscarinic acetylcholine receptor or B-adrenoceptor receptors and then would further need to determine which of the claimed compounds would provide treatment of the disease.

**The level of the skill in the art:** The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compounds of claim 1 for the treatment of any disease. As a result necessitating one of ordinary skill to perform an exhaustive search for which diseases can be treated by which compound of claim 1 in order to practice the claimed invention.

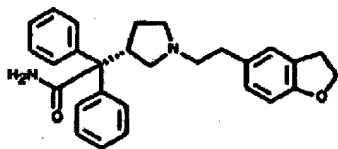
Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling

disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, one of ordinary skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compounds of the instant claims, with no assurance of success.

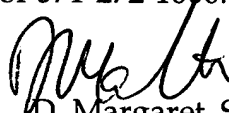
*Allowable Subject Matter*

7. Claims drawn to compounds to formula III wherein R4 is alkylene would appear to be free of prior art. The closest prior art is Cross (US Patent #5340831& 5096890), Allen (US Patent #5837724) and Venn (Chromatographia, Vol 50(7/8), PP 407-414, 1999). However these references teach compounds such as darifenacin



If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thomas McKenzie can be reached on 571-272-0670. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

  
D. Margaret Seaman  
Primary Examiner  
Art Unit 1625

dms